memo

(1) MR → MV SURVEYS
(2) MARKETING SUBCOMMITTEE
(3) INTRODUCE OXY IR
(4) PUBLISH - P.R.
(5) PERCOCET

to: P. Goldenheim
R. Reder
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from: R. Kaiko

dept: Medical

subject: OXYCONTIN CLAIMS LISTING

date: October 4, 1993

over other opioids?

In preparation for our meeting of 10/5 regarding Oxycontin claims please find below a listing of what our claims might be over oral morphine and their respective sources of support.

Oxycontin claims over oral morphine/*support sources*

ANALGESIC AND

I. PRIMARY CLAIM: "MOST EFFICIENTLY TITRATABLE LONG-ACTING STRONG ANALGESIC"

A. short half-life of elimination

This is well established in the literature.

and efficient

B. rapidly attains steady-state plasma oxycodone levels → hence quick titrate for better patient contr

According to basic pharmacokinetic principles, a short half-life provides for rapid attainment of steady-state. Additionally we have two steady-state studies already demonstrating this claim.

C. rapidly attains stable pain control → how quickly? Can we estimate

This is inferred from above pharmacokinetics: a drug with a short half-life invariably achieves steady-state rapidly and concurrently achieves stable pharmacodynamics. Additionally, ongoing efficacy studies are likely to confirm this. While the above three claims are not, in themselves, superiority claims over ~~morphine~~, they are components of the primary claim over ~~morphine~~ and superiority claims over any drug with a longer elimination half-life (e.g., fentanyl, methadone, levorphanol, buprenorphine).

other opioids

D. rapidly titratable to the "right dose" → Can we say how quickly we will get to the right dose

This follows from the above sections; any drug with a short half-life can be safely and appropriately titrated on a daily basis.

E. high oral bioavailability

Numerous published studies have established that morphine has a low oral bioavailability (20-40%) while several other studies have established that oxycodone has a high oral bioavailability (50-90%).

What % is tied to the 1st pass effect? This may be an advantage re oral morphine

F. less variation in bioavailability

This is inferred in that any drug with a high oral bioavailability will inherently have less variation associated with its bioavailability than a drug with low oral bioavailability. On the other hand there have been no studies specifically designed to demonstrate this comparison for oxycodone and morphine. We should find examples to illustrate this within our own bioavailability/bioequivalency/pharmacokinetic database, if possible, and begin to develop support for this claim well before the completion of our Phase III pk/pd comparative evaluations of Oxycontin and MS Contin. In addition to retrospective analyses of our Phase I oral morphine and oxycodone studies, we should carefully evaluate the published literature to support this claim.

G. less variation in plasma oxycodone concentrations

Please see the preceding section.

H. less variation in pain control

This is inferred from the above two claims in that any such drug with less variation in bioavailability and in plasma concentration will, according to basic pharmacokinetic/pharmacodynamic principles, have less variation associated with its pharmacodynamics.

I. fewer patients under- or overdosed upon initiation of Oxycontin

While one would predict this based on its unique combination of a high oral bioavailability and short half-life, this claim would need to be clinically demonstrated. While this may be difficult to demonstrate, we have a number of opportunities in those studies involving both oxycodone and morphine, although none have really been designed to address this question. This is particularly a problem if those numerous conversion factors from prior analgesics to oxycodone and to morphine differ substantially in their validity or ability to provide initial equianalgesic oxycodone and morphine dosages. One would hope to see comparable average pharmacodynamics but with a "sharper" bell-shaped curve for oxycodone than for morphine (i.e., fewer outliers).

important

J. the first dose is the "right dose" in more patients

Please see above section.

K. less variation in analgesia and other opioid effects once stabilized

Please see above section but appreciate that this is primarily related to the higher oral bioavailability and its resulting lack of variability. Also appreciate that the issue of relative potency would be irrelevant in the demonstration of this claim but that this may be just as elusive as the above two claims.

L. less need for dose adjustment, once stabilized

As directly above, this is merely another way of expression of the same underlying phenomena.

M. the only strong oral analgesic with both a short elimination half-life and a high oral bioavailability

This is from the literature as summarized earlier.

II. SECONDARY CLAIM: "ONLY LONG-ACTING STRONG ANALGESIC IN BOTH STEPS 2 AND 3 OF THE W.H.O. ANALGESIC STEP-LADDER"

We have been told that the in-press next edition of the WHO Cancer Pain Relief monograph has oxycodone as the only opioid analgesic in both steps 2 and 3 of the analgesic step-ladder; it is of concern that this next edition has languished in the Geneva headquarters so long; we need to re-establish our earlier understanding and, if necessary, facilitate the release of the document. Dr. Ventafridda, now working in the Cancer Unit of the WHO, may be key toward documenting this claim.

Should be more important than just a [illegible] secondary claim

A. eliminates the need to switch primary analgesics as patients' analgesic needs increase

This is self-evident. In addition, the results of studies of two pain model populations, osteoarthritis and low back pain patients should provide for demonstrations that Oxycontin can be added to NSAIDs and replace fixed combination products normally used in step 2 of the ladder. Our studies in cancer pain document the benefits of Oxycontin in step 3.

B. simplifies cancer pain management

This is self-evident.

III. TERTIARY CLAIM: "FOR SPECIAL PATIENT POPULATIONS"

A. no known active metabolites that accumulate in renal impairment

The combination of the literature as well as our own study may provide for this claim, but it is highly likely that our own study will need to be definitive in terms of Oxycontin in order to use the literature regarding morphine.

may be our hook
Will patients
for switching from
morphine

B. insignificant alterations in bioavailability in hepatic dysfunction

As above.

C. insignificant alterations in bioavailability in the elderly

As above.

IV. TERTIARY CLAIM: "PREFERRED BY MORE PATIENTS"

This is the issue of "image" and the likely willingness of patients to receive oxycodone rather than morphine solely on the basis of "the myths of morphine". We can begin adding an up-front questionnaire to our studies involving both drugs and/or request a separate designed survey.

We should also
measure and analyze
patient preference data

RK:df